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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/767,088	GURNEY ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *3-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 9-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The response filed November 3, 2003 has been entered.

Claims 1-17 are pending in the instant application.

Applicants' election with traverse of Group I, Claims 1-17, in the response filed November 3, 2003 is acknowledged. The elected invention is drawn to a transgenic mouse comprising a polynucleotide encoding a human wild-type tau protein, wherein said tau protein is the isoform that is 352 amino acids in length.

Claims 3-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the response filed November 3, 2003. At page 4 of the response, Applicants assert that no serious burden would be imposed on the Examiner by combining several of the groups. No support or reasoning is offered for this assertion. Moreover, Applicants do not indicate which groups could be combined so that no serious burden would be imposed. Applicants are referred back to pages 5-6 of the Office Action mailed 10/1/03 which provides detailed reasons why a search and examination of all 12 inventions in a single patent application imposes a serious burden on the Examiner.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The Post Office addresses are not provided.

Specification

The disclosure is objected to for citing the wrong statute in paragraph [0001] where the statute "35 U.S.C. §112(e)" is cited instead of 35 U.S.C. §119(e). Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

Claim 16 is directed to a method of screening for a drug that blocks hyperphosphorylation of tau. The claim requires the use of a transgenic mouse expressing hyperphosphorylated tau protein. Claim 17 is directed to a method of screening for a drug that blocks formation of filamentous aggregates of tau. The claim requires the use of a transgenic mouse expressing human tau protein forming filamentous aggregates.

The specification does not provide a written description of a transgenic mouse expressing hyperphosphorylated human tau protein as recited in Claim 16 nor a transgenic mouse expressing human tau protein forming filamentous aggregates as recited in Claim 17. In the absence of a clear written

description of the mice to be used in the screening assays, the written description requirement is not satisfied for the claimed methods of screening.

Enablement

Claims 1, 2, and 9-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

The following factors have been considered.

Nature of the invention. The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein.

Amount of direction or guidance presented and the presence or absence of working examples. The instant specification discloses the generation of transgenic mice using the wild-type tau isoform 383 amino acids in length. The specification also discloses two types of transgenic mice each having a point mutation within the 383 amino acid isoform of tau (V337M and P332L).

State of the prior art and predictability of the art. The specification fails to provide an enabling disclosure for the preparation of the claimed transgenic mice, because the phenotype of a transgenic animal cannot be predicted.

The specification fails to provide an enabling disclosure for the preparation of the claimed transgenic mice because the guidance offered in the specification is not sufficient to teach one of skill in the art how to prepare the claimed transgenic mice exhibiting an appropriate phenotype. The mere capability to perform gene transfer in any given species is not enabling for the claimed transgenic animals because the desired phenotype cannot be predictably achieved by simply introducing a construct as recited in the claims. While gene transfer techniques are well-developed for a number of species, including the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse cannot necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). Wall (1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements, and may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). In the absence of specific guidance, the production of a transgene-dependent phenotypic alteration

resulting from the introduction of a nucleic acid construct as recited in the claim, is unpredictable. Thus, given the limited working examples, the existence of any phenotypic alteration resulting from the introduction of a tau transgene into mice, is highly unpredictable. Given the limited working examples and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the claimed transgenic mice.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

Accordingly, given the demonstrated lack of predictability in the art, the limited guidance provided in the specification, the state of the prior art, the broad scope of the claims, the quantity of experimentation needed, and the limited applicable working examples, one of skill in the art would not be able to make and use the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-13 are indefinite in their recitation of "5' flanking sequence" and "the initial, noncoding portion of the second PrP exon" because the metes and bounds of these regions are not clearly set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) The invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in—
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, and 9-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Zehr et al. (October 1999, Society for Neuroscience Abstracts 25(1): 447.1).

The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein.

Zehr et al. disclose the production and characterization of transgenic mice expressing human Tau polypeptides. The authors generated multiple lines of transgenic mice expressing one of four different tau cDNAs (wild-type 3 repeat, wild-type 4 repeat, V337M 3 repeat, and P301L 4 repeat). Expression of the tau polypeptides was driven by the mouse prion promoter. The highest levels of expression were found in the hippocampus, cortex, striatum, and the thalamus.

Thus, the claimed invention is disclosed in the prior art.

Claims 1, 2, and 9-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Ishihara et al. (October 1999, Society for Neuroscience Abstracts 25(1): 447.2).

The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein.

Ishihara et al. disclose the production and characterization of transgenic mice expressing human Tau polypeptides. The authors overexpressed the 352 amino acid isoform of human tau in the central nervous system of mice using a transgene containing a tau cDNA driven by a mouse prion protein promoter. They report that the transgenic mice acquired an age-dependent tauopathy similar to FTDP-17, PSP, and ALS/PDC. They further observed argyrophilic intraneuronal inclusions of 10-20 nm filaments. Brain and spinal cord tau became insoluble and abnormally phosphorylated in the transgenic mice. The authors point out that, since similar tau pathology occurs in Alzheimer's disease (AD), studies of these transgenic mice may elucidate mechanisms that lead to the selective degeneration of neurons in AD.

Thus, the claimed invention is disclosed in the prior art.

Claims 1, 2, and 9-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Ishihara et al. (November 1999, Neuron 24: 751-762).

The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein.

Ishihara et al. disclose the production and characterization of transgenic mice expressing human Tau polypeptides. The authors overexpressed the 352 amino acid isoform of human tau in the central nervous system of mice using a transgene containing a tau cDNA driven by a mouse prion protein promoter. They report that the transgenic mice acquired an age-dependent tauopathy similar to FTDP-17, PSP, and ALS/PDC. They further observed argyrophilic intraneuronal inclusions of 10-20 nm filaments. Brain and spinal cord tau became insoluble and hyperphosphorylated in the transgenic mice. The authors

point out that, since similar tau pathology occurs in Alzheimer's disease (AD), studies of these transgenic mice may elucidate mechanisms that lead to the selective degeneration of neurons in AD.

Thus, the claimed invention is disclosed in the prior art.

Claims 1, 2, and 9-13 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,475,723 (Hutton et al.).

The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein.

Hutton et al. teach that transgenic mammals expressing the Tau polypeptide will exhibit a Tau pathology (column 2, lines 20-21). The reference further teaches that a brain-specific promoter should be used to drive expression of the Tau polypeptide (column 2, lines 23-24). In particular, the reference teaches that the prion gene promoter should be used (column 6, line 54). At column 6, lines 40-42, the reference teaches that regulatory nucleic acid sequences provide expression of the Tau polypeptide in sufficient levels to produce a Tau pathology.

Thus, the claimed invention is disclosed in the prior art.

Claims 1, 2, and 9-13 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,664,443 (Hutton et al.).

The claims are directed to a transgenic mouse comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said mouse expresses human tau protein.

Hutton et al. disclose transgenic mice expressing the human Tau polypeptide under control of the mouse prion promoter. See Examples 5-7. Transgenic mice expressing the wild-type 441 amino acid isoform of tau, the wild-type 383 amino acid isoform, and the P301L mutant form of tau were produced.

The reference further discloses that the mice exhibited a Tau pathology. The mice developed motor and behavioral disturbances and tau-positive neurofibrillary tangles (NFT) were identified in the diencephalon, brainstem, cerebellar nuclei, and spinal cord (column 18, line 44 through column 19, line 27).

Thus, the claimed invention is disclosed in the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishihara et al. (October 1999, Society for Neuroscience Abstracts 25(1): 447.2).

Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishihara et al. (Novewmber 1999, Neuron 24: 751-762).

The claims are directed to a method for screening for a drug for treatment of a neurodegenerative disease, or for a drug that blocks hyperphosphorylation of tau, or for a drug that blocks formation of filamentous aggregates of tau.

Ishihara et al. disclose the production and characterization of transgenic mice expressing human Tau polypeptides. The authors overexpressed the 352 amino acid isoform of human tau in the central nervous system of mice using a transgene containing a tau cDNA driven by a mouse prion protein promoter. They report that the transgenic mice acquired an age-dependent tauopathy similar to FTDP-17, PSP, and ALS/PDC. They further observed argyrophilic intraneuronal inclusions of 10-20 nm filaments. Brain and spinal cord tau became insoluble and hyperphosphorylated in the transgenic mice. The authors

point out that, since similar tau pathology occurs in Alzheimer's disease (AD), studies of these transgenic mice may elucidate mechanisms that lead to the selective degeneration of neurons in AD.

Given the phenotype of the disclosed transgenic mice and further given that said phenotype correlates with a pathological hallmark of a number of neurodegenerative diseases, it would have been obvious to use the mice to screen for drugs that may be useful in treating a neurodegenerative disease. Moreover, given the observed hyperphosphorylated tau protein in the brain and spinal cord of the transgenic mice, the skilled artisan would have been motivated to use the mice to screen for drugs that block this pathological process. Likewise, given the observed formation of filamentous inclusions in the transgenic mice, the skilled artisan would have been motivated to use the mice to screen for drugs that block this pathological process.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (571) 272-0548.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER